PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:
A61K 9/00, 9/12	A1	WO 96/18384
		(43) International Publication Date: 20 June 1996 (20.06.96)

(21) International Application Number: PCT/EP95/04824

(22) International Filing Date: 8 December 1995 (08.12.95)

(30) Priority Data:
9425160.0 10 December 1994 (10.12.94) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SAPSFORD, Andrew [GB/GB]; Glaxo Research and Development, Park Road, Ware, Hertfordshire SG12 0DP (GB). SAVAGE, Andrew, Patrick [GB/GB]; Glaxo Research and Development, Park Road, Ware, Hertfordshire SG12 0DP (GB).

(74) Agent: DAWSON, Hugh, B.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: PROPELLANT MIXTURE FOR AEROSOL FORMULATION

(57) Abstract

This invention relates to aerosol formulations of use the administration of medicaments by inhalation in particular a pharmaceutical aerosol formulation which comprises (a) 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof as propellant, (b) 1,1,2,2,3-pentafluoropropane as co-propellant; and (c) particulate medicament. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation as defined is also described.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

PROPELLANT MIXTURE FOR AEROSOL FORMULATION

This invention relates to aerosol formulations of use in the administration of medicaments by inhalation.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol.

The most commonly used aerosol propellants for medicaments have been CCl_3F (propellant 11) in admixture with CCl_2F_2 (propellant 12) and $CF_2Cl.CF_2Cl$ (propellant 114). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrogen-containing chlorofluorocarbons and fluorocarbons and a number of medicinal aerosol formulations using such propellant systems have been disclosed in, for example, EP 0372777, WO91/04011, W091/11173, W091/11495, W091/14422, W092/00061, W092/00062 and W092/00107.

These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome the problems associated with the use of the new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. These applications all propose the addition of a wide range of adjuvants such as alcohols, alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids, polyethoxylates etc) and even conventional chlorofluorocarbon propellants in small amounts to minimise potential ozone damage.

Surprisingly, we have now found that mixtures of a non ozone-depleting propellant and a specific fluorinated hydrocarbon may be employed as propellant systems suitable for use in pharmaceutical aerosol compositions.

There is thus provided in one aspect of the invention an aerosol formulation comprising:

(a) 1,1,1,2-tetrafluoroethane (CF_3CH_2F), 1,1,1,2,3,3,3-heptafluoro-n-propane (CF_3CHFCF_3) or mixtures thereof as propellant;

(b) 1,1,2,2,3-pentafluoropropane as co-propellant; and

(c) particulate medicament.

Generally, the ratio of propellant : co-propellant is in the range of about 30 : 70 to about 95 : 5, preferably 50 : 50 to 90 : 10 by weight, especially 50 : 50 to 80 : 20, for example 75 : 25 (w/w).

Medicaments which may be administered in aerosol formulations according to the invention include any drugs useful in inhalation therapy which may be presented in a form which is substantially completely insoluble in the selected propellant system. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. dilitiazem; antiallergics, e.g. cromolyn, cromogylcate or nedocromil; antibiotics, e.g. cephalosporins, penicillins, streptomycin, sulphonamides or tetracyclines; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide, fluticasone, tipredane, budesonide, triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, epinephrine, fenoterol, formoterol, isoprenaline, isoproterenol, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, repoterol, rimiterol, salbutamol, salmeterol, terbutaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium bromide; hormones, e.g. cortisone, hydrocortisone or prednisolone; and therapeutic proteins and peptides, e.g. glucagon or insulin. It will be clear to a person skilled in the art that, where appropriate, the medicaments will be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl

esters) or as solvates (eg hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred medicaments for administration using aerosol formulations in accordance with the invention include bronchodilators and anti-inflammatory steroids of use in the treatment of asthma by inhalation therapy, for example salbutamol (e.g. as the sulphate), salmeterol (e.g. as the hydroxynaphthoate known as salmeterol xinafoate), beclomethasone dipropionate or a solvate thereof, fluticasone propionate or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2pyridinyl)ethoxy]hexyl]amino]methyl] benzenemethanol.

The particle size of the particulate medicament should be such as to permit inhalation of substantially all of the medicament into the lungs upon administration of the aerosol formulation and will thus desirably be less than 20 microns, preferably in the range 1 to 10 microns, e.g. 1 to 5 microns. The particle size of the medicament may be reduced by conventional means, for example by milling or micronisation.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005-5% w/w, especially 0.01-1.0% w/w, of medicament relative to the total weight of the formulation.

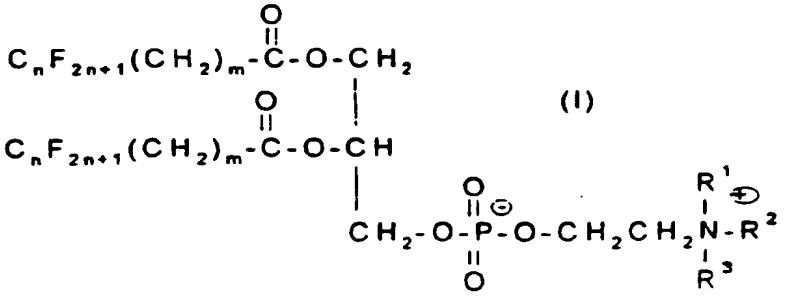
It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3. As used herein "substantially free" means less than 1% w/w based upon the propellant system, in particular less than 0.5%, for example 0.1% or less.

The propellant may optionally contain an adjuvant having a higher polarity and/or a higher boiling point than the propellant. Polar adjuvants which may be used include (e.g. C_{2-6}) aliphatic alcohols and polyols such as ethanol, isopropanol and propylene glycol, preferably ethanol. In general only small quantities of polar adjuvants (e.g. 0.05 - 3.0% w/w) may be required to improve

the stability of the dispersion - the use of quantities in excess of 5% w/w may tend to dissolve the medicament. Formulations in accordance with the invention may preferably contain less than 1% w/w, e.g. about 0.1% w/w, of polar adjuvant. However, the formulations of the invention are preferably substantially free of polar adjuvants, especially ethanol. Suitable volatile adjuvants include saturated hydrocarbons such as propane, n-butane, isobutane, pentane and isopentane and alkyl ethers such as dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile adjuvant, for example 1 to 30% w/w of a volatile saturated C_{1-6} hydrocarbon.

Optionally, the aerosol formulations according to the invention may further comprise one or more surfactants. The surfactants must be physiologically acceptable upon administration by inhalation. Within this category are included surfactants such as oleic acid, sorbitan trioleate (Span R 85), sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil and sunflower seed oil. Preferred surfactants are lecithin, oleic acid and sorbitan trioleate.

An alternative class of surfactants are described in EP 0478686, especially surfactants of formula (I)



(I)

wherein n is an integer of 1 to 18, especially 2 to 12; m is an integer of 0 to 17, especially 0 to 11; and R^1, R^2 and R^3 are each independently a hydrogen atom or a C_{1-4}alkyl group.

Particularly preferred surfactants of formula (I) are the fluorinated phosphatidylcholines wherein R^1, R^2 and R^3 each represent methyl, n is an integer of 4 to 8, especially 4 or 6, and m is an integer of 4 to 10, especially 4 or 6.

If desired, the surfactant may be incorporated into the aerosol formulation in the form of a surface coating on the particulate medicament. In this case, the use of substantially non-ionic surfactants which have reasonable solubility in substantially non-polar solvents is frequently advantageous since it facilitates coating of the medicament particles using solutions of surfactant in non-polar solvents in which the medicament has limited or minimal solubility.

The amount of surfactant employed in coating the particulate medicament is desirably in the range 0.1 to 10% w/w, preferably 1 to 10% w/w, relative to the medicament. Where the surfactant is present as a surface coating, the amount may advantageously be chosen such that a substantially monomolecular coating of surfactant is formed. However, it is preferable that the formulations of the invention are substantially free of surfactants, i.e. contain less than an effective stabilising amount of a surfactant such as less than 0.0001% by weight of medicament.

The formulations of the invention may be prepared by dispersal of the medicament in the selected propellant and/or co-propellant in an appropriate container, e.g. with the aid of sonication. Preferably the particulate medicament is suspended in co-propellant and filled into a suitable container. The valve of the container is then sealed into place and the propellant introduced by pressure filling through the valve in the conventional manner. Surprisingly, the aerosol formulations according to the invention have been found to be easily redispersed by mild agitation to provide suspensions with excellent delivery

characteristics suitable for use in pressurised inhalers, even after prolonged storage.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product. Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

The formulations according to the invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated, which container is closed with a metering valve. The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK356) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser^{TM}).

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method the particulate medicament is first suspended in the co-propellant. The drug suspension is then filled into the empty canisters, valves crimped on and then propellant is

pressure filled into the canisters through the valves in conventional manner. Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channelling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 puffs each time.

The following non-limitative Examples serve to illustrate the invention.

Example 1

Micronised salmeterol xinafoate (hydroxynaphthoate, 8.7mg) was weighed into a clean, dry glass bottle together with 1,1,2,2,3-pentafluoropropane (1.3g, 1ml). The bottle was sealed by crimping a valve in place. Propellant 1,1,1,2-tetrafluoroethane (20.7g, 17ml) was added, under pressure, through the valve. The resultant inhaler delivers 25µg of salmeterol xinafoate (hydroxynaphthoate)

per actuation (200 75mg actuations per bottle). The ratio of propellant (CF_3CH_2F) to co-propellant ($CHF_2CF_2CH_2F$) was 17 : 1 (v/v).

Example 2

Micronised salmeterol xinafoate (hydroxynaphthoate, 8.7mg) was weighed into a clean, dry glass bottle together with 1,1,2,2,3-pentafluoropropane (5.2g, 4ml). The bottle was sealed by crimping a valve in place. Propellant 1,1,1,2-tetrafluoroethane (17.1g, 14ml) was added, under pressure, through the valve. The resultant inhaler delivers 25µg of salmeterol xinafoate (hydroxynaphthoate) per actuation (200 75mg actuations per bottle). The ratio of propellant (CF_3CH_2F) to co-propellant ($CHF_2CF_2CH_2F$) was 14 : 4 (v/v).

Example 3

Micronised salmeterol xinafoate (hydroxynaphthoate, 4mg) was weighed into a clean, dry aluminium aerosol canister (8ml) together with co-propellant 1,1,2,2,3-pentafluoropropane (2g). The canister was sealed by crimping a valve in place and propellant 1,1,1,2-tetrafluoroethane (10g) was added, under pressure, through the valve. The resultant inhaler delivers 25µg of salmeterol hydroxynaphthoate per actuation (120 75mg actuations per can).

Examples 4 to 7

Inhalers were prepared as described in Example 3 containing propellant (CF_3CH_2F) to co-propellant ($CHF_2CF_2CH_2F$) in the ratios of 9 : 3, 8 : 4, 7 : 5 and 6 : 6 (w/w) (Examples 4, 5, 6 and 7 respectively).

Example 8

Micronised salbutamol (base) (24mg) is homogenised with the aid of sonication in a solution of oleic acid (2.4mg) in the co-propellant 1,1,2,2,3-pentafluoropropane (4.7g) and filled into a clean, dry aluminium aerosol canister. The canister is sealed by crimping a valve in place. Propellant 1,1,1,2-tetrafluoroethane (14.1g) is added, under pressure, through the valve.

The resultant inhaler delivers 100 microgram salbutamol per 75mg actuation. The ratio of propellant (CF_3CH_2F) to co-propellant ($CHF_2CF_2CH_2F$) was 75 : 25 (w/w).

Examples 9 to 11

Inhalers are prepared as described in Example 8 containing propellant (CF_3CH_2F) and co-propellant ($CHF_2CF_2CH_2F$) in the ratios 70 : 30, 50 : 50 and 95 : 5 (w/w) (Examples 9, 10 and 11 respectively).

Example 12

Micronised salbutamol (base) (24mg) is homogenised with the aid of sonication in a solution of oleic acid (2.4mg) in the co-propellant 1,1,2,2,3-pentafluoropropane (5.3g) and filled into a clean, dry aluminium aerosol canister. The canister is sealed by crimping a valve in place. Propellant 1,1,1,2,3,3,3-heptafluoro-n-propane (15.9g) is added, under pressure, through the valve. The resultant inhaler delivers 100 microgram salbutamol per 75mg actuation. The ratio of propellant (CF_3CHFCF_3) to co-propellant ($CHF_2CF_2CH_2F$) was 75 : 25 (w/w).

Examples 13 to 15

Inhalers are prepared as described in Example 12 containing propellant (CF_3CHFCF_3) to co-propellant ($CHF_2CF_2CH_2F$) in the ratios 70 : 30, 50 : 50 and 95 : 5 (w/w) (Examples 13, 14 and 15 respectively).

Example 16

Micronised fluticasone propionate (4mg) is weighed into a clean, dry aluminium aerosol canister (8ml) together with co-propellant 1,1,2,2,3-pentafluoropropane (3.1g). The canister is sealed by crimping a valve in place. Propellant 1,1,1,2-tetrafluoroethane (9.3g) is added, under pressure, through the valve. The resultant inhaler delivers 25µg of fluticasone propionate per actuation (120

75mg actuations per can). The ratio of propellant (CF_3CH_2F) to co-propellant ($CHF_2CF_2CH_2F$) is 9:3w/w.

Example 17

Micronised salmeterol xinafoate (hydroxynaphthoate, 4mg) and micronised fluticasone propionate (8mg) are weighed into a clean, dry aluminium aerosol canister (8ml) together with co-propellant 1,1,2,2,3-pentafluoropropane (3.1g). The canister is sealed by crimping a valve in place. Propellant 1,1,1,2-tetrafluoroethane (9.3g) is added, under pressure, through the valve. The resultant inhaler delivers 25µg salmeterol xinafoate (hydroxynaphthoate) and 50µg fluticasone propionate per actuation (120 75mg actuations per can). The ratio of propellant (CF_3CH_2F) to co-propellant ($CHF_2CF_2CH_2F$) is 9:3w/w.

CLAIMS

1. A pharmaceutical aerosol formulation comprising
(a) 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof as propellant;
(b) 1,1,2,2,3-pentafluoropropane as co-propellant; and
(c) particulate medicament.

2. A formulation according to claim 1 wherein the ratio of propellant:co-propellant is about 30:70 to about 95:5 by weight.

3. A formulation according to claim 2 wherein the ratio of propellant:co-propellant is about 50:50 to about 80:20 by weight.

4. A formulation according to any one of claims 1 to 3 wherein the propellant comprises 1,1,1,2-tetrafluoroethane.

5. A formulation according to any one of claims 1 to 3 wherein the propellant comprises 1,1,1,2,3,3,3-heptafluoro-n-propane.

6. A formulation according to any one of claims 1 to 5 wherein the medicament is an anti-allergic, a bronchodilator or an anti-inflammatory steroid.

7. A formulation according to any one of claims 1 to 6 wherein the medicament is salmeterol xinafoate.

8. A formulation according to any one of claims 1 to 6 wherein the medicament is salbutamol sulphate.

9. A formulation according to any one of claims 1 to 6 wherein the medicament is fluticasone propionate.

10. A formulation according to any one of claims 1 to 6 wherein the medicament is beclomethasone dipropionate of a physiolgically acceptable solvate thereof.

11. A formulation according to any one of claims 1 to 6 wherein the medicament is formoterol, cromoglycate, terbutaline, reproterol or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzemethanol budesonide, triamcinolone acetonide or a physiologically acceptable salt or solvate thereof.

12. A formulation according to any one of claims 1 to 11 wherein the medicament is present in an amount of 0.005 to 10% w/w relative to the total weight of the formulation.

13. A formulation according to claim 12 wherein the medicament is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

14. A formulation according to any one of claims 1 to 13 which contains two or more particulate medicaments.

15. A formulation according to claim 14 which contains salbutamol or salmeterol or a physiologically acceptable salt thereof in combination with an anti-inflammatory steroid or an anti-allergic.

16. A formulation according to claim 15 which contains salmeterol or salbutamol or a physiologically acceptable salt thereof in combination with fluticasone propionate or beclomethasone dipropionate or a physiologically acceptable solvate thereof.

17. A formulation according to any one of claims 1 to 16 comprising an adjuvant having a higher polarity and/or a boiling point than the propellant.

18. A formulation according to claim 17 wherein the adjuvant having a higher polarity than the propellant is present in an amount of 0.05 to 5% w/w based upon the propellant and co-propellant.

19. A formulation according to any one of claims 1 to 18 comprising a surfactant.

20. A canister suitable for delivering a pharmaceutical aerosol formulation which comprises a container capable of withstanding the vapour pressure of the propellant used which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises (a) 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof as propellant, (b) 1,1,2,2,3-pentafluoropropane as co-propellant, and (c) a particulate medicament.

21. A canister according to claim 20 wherein the container is a metal can.

22. A canistrer according to claim 21 wherein the container is an aluminium can.

23. A canister according to claim 21 or 22 wherein the container is plastics-coated.

24. A metered dose inhaler which comprises a canister according to any one of claims 20 to 24 fitted into a suitable channelling device.

25. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation according to any one of claims 1 to 18.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/04824

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 02150 (DU PONT) 4 February 1993 see page 13, column 6, line 8 - line 12; table 1 ---	1-25
Y	US,A,5 314 926 (ROBIN MARK L ET AL) 24 May 1994 see column 3, line 1 - line 61 ---	1-25
Y	WO,A,94 03153 (GLAXO GROUP LTD ;TAYLOR ANTHONY JAMES (GB); NEALE PHILIP JOHN (GB)) 17 February 1994 see claims 1-13 ---	1-25
Y	WO,A,93 11745 (GLAXO GROUP LTD) 24 June 1993 see claims 1-16 --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 1996	02.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Foerster, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/04824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 11743 (GLAXO GROUP LTD) 24 June 1993 see claims 1-22	1-25
A	WO,A,93 18746 (ASTA MEDICA AG) 30 September 1993 see claims 1-12	1-25
A	WO,A,91 14422 (MINNESOTA MINING & MFG) 3 October 1991 cited in the application see claims 1-9	1-25

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 95/04824

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9302150	04-02-93	AU-B-	2343692	23-02-93
		CN-A-	1068841	10-02-93
		DE-D-	69204290	28-09-95
		EP-A-	0595937	11-05-94
		EP-A-	0661365	05-07-95
US-A-5314926	24-05-94	US-A-	5278196	11-01-94
		AU-B-	6589794	11-10-94
		EP-A-	0690887	10-01-96
		WO-A-	9421718	29-09-94
		ZA-A-	9401859	17-10-94
WO-A-9403153	17-02-94	AU-B-	4705093	03-03-94
		CA-A-	2141039	17-02-94
		CN-A-	1088436	29-06-94
		EP-A-	0658101	21-06-95
		JP-T-	7509475	19-10-95
		ZA-A-	9305477	23-02-94
WO-A-9311745	24-06-93	AT-T-	128350	15-10-95
		AU-B-	663906	26-10-95
		AU-B-	3085292	19-07-93
		CA-A-	2125665	24-06-93
		DE-D-	69205177	02-11-95
		EP-A-	0616525	28-09-94
		JP-T-	7501811	23-02-95
		NZ-A-	246046	21-12-95
		ZA-A-	9209618	09-08-93
		AP-A-	402	22-08-95
		AU-B-	663904	26-10-95
		AU-B-	3085092	19-07-93
		AU-B-	663905	26-10-95
		AU-B-	3085192	19-07-93
		BG-A-	98803	28-02-95
		CA-A-	2125666	24-06-93
		CA-A-	2125667	24-06-93
		CN-A-	1075078	11-08-93
		CN-A-	1075079	11-08-93
		CZ-A-	9401430	15-03-95
		WO-A-	9311743	24-06-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ional Application No
PCT/EP 95/04824

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9311745		WO-A-	9311744	24-06-93
		EP-A-	0616523	28-09-94
		EP-A-	0616524	28-09-94
		HU-A-	67534	28-04-95
		JP-T-	7502033	02-03-95
		JP-T-	7502034	02-03-95
		NO-A-	942185	10-06-94
		NZ-A-	246044	26-01-96
		OA-A-	9926	15-09-94
		SK-A-	67494	08-03-95
WO-A-9311743	24-06-93	AP-A-	402	22-08-95
		AU-B-	663904	26-10-95
		AU-B-	3085092	19-07-93
		BG-A-	98803	28-02-95
		CA-A-	2125667	24-06-93
		CZ-A-	9401430	15-03-95
		EP-A-	0616523	28-09-94
		HU-A-	67534	28-04-95
		JP-T-	7502033	02-03-95
		NO-A-	942185	10-06-94
		NZ-A-	246044	26-01-96
		OA-A-	9926	15-09-94
		SK-A-	67494	08-03-95
		ZA-A-	9209617	22-03-94
		AU-B-	663905	26-10-95
		AU-B-	3085192	19-07-93
		CA-A-	2125666	24-06-93
		WO-A-	9311744	24-06-93
		EP-A-	0616524	28-09-94
		JP-T-	7502034	02-03-95
		AT-T-	128350	15-10-95
		AU-B-	663906	26-10-95
		AU-B-	3085292	19-07-93
		CA-A-	2125665	24-06-93
		CN-A-	1075078	11-08-93
		CN-A-	1075079	11-08-93
		DE-D-	69205177	02-11-95
		WO-A-	9311745	24-06-93
		EP-A-	0616525	28-09-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 95/04824

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9311743		JP-T-	7501811	23-02-95
		NZ-A-	246046	21-12-95
WO-A-9318746	30-09-93	DE-A-	4230876	23-09-93
		AU-B-	3745993	21-10-93
		CA-A-	2129855	18-09-93
		EP-A-	0630229	28-12-94
		FI-A-	944257	14-09-94
		HU-A-	68223	28-06-95
		JP-T-	7508506	21-09-95
		NO-A-	943305	07-09-94
		SK-A-	385892	12-04-95
		US-A-	5415853	16-05-95
		ZA-A-	9301907	06-10-93
WO-A-9114422	03-10-91	AU-B-	654813	24-11-94
		AU-B-	7668691	21-10-91
		CA-A-	2077354	24-09-91
		DE-D-	69109284	01-06-95
		DE-T-	69109284	24-08-95
		EP-A-	0526481	10-02-93
		EP-A-	0636362	01-02-95
		ES-T-	2071306	16-06-95
		US-A-	5118494	02-06-92